Tolerance mechanisms of AIT

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Abstract: Allergen immunotherapy (AIT) is the only curative treatment for allergic diseases. It induces immune tolerance together with the reduction of the symptoms of asthma and allergic rhinitis patients. The common routes for the application of AIT for respiratory allergens are subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT). SCIT improves the symptoms of asthma and rhinitis and increase the quality of life.

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Tolerance mechanisms of AIT

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Allergen immunotherapy (AIT) is the only curative treatment for allergic diseases. It induces immune tolerance together with the reduction of the symptoms of asthma and allergic rhinitis patients. The common routes for the application of AIT for respiratory allergens are subcutaneous immunotherapy (SCIT) and sublingual immunotherapy

(SLIT). SCIT improves the symptoms of asthma and rhinitis and increase the quality of life. SLIT is a non-invasive, well-tolerated and efficient treatment for respiratory allergies.[1] In this issue of Allergy, Heeringa et al. report that sublingual immunotherapy induces IgG2 and IgG4 B-cell memory. Although, it was shown that AIT has long lasting beneficial effects, there is still relatively little known on how this affects the B cell memory. This question was studied longitudinally before, during and after SLIT for grass pollen allergy in moderate to severe seasonal allergic rhinitis.[2]

Despite its relative success, AIT faces several challenges, including worldwide standardization, limitations in efficacy, sometimes severe side effects, low patient adherence, and high costs due to the long duration (3 to 5 years) of treatment. Various approaches are being pursued to answer all of the above challenges. Grass pollen SLIT has been recommended in this study as a pre- and co-seasonal course starting 4 months prior to the hay fever season, confirmed by meta-analyses as clinically effective. Patients are exposed to grass pollens during the spring season, in this study patients received a 4-month pre-seasonal treatment regimen that would avoid the risk of adding to excessive and unpredictable allergen loads during the season.[3] Based on analysis of symptom scores, this approach was highly effective. Prolonged treatment (duration >12 months) is known to have beneficial effects on symptom and medication scores. The fact that some immunological effects were delayed, only occurring after the second or third treatment year as observed for serum ragweed pollen (RGP)-specific IgG2 levels, or continuing to rise after consecutive treatment as for serum RGP-specific IgG4 levels, supports these findings. It was demonstrated that SLIT for grass pollen allergy not only has long-term beneficial clinical effects, but also results in sustained systemic effects on the immune system. SLIT induced a rapid and prolonged increase in RGP-specific serum IgG4 accompanied by an increase in the frequency of peripheral blood IgG4+ memory B cells. Furthermore, repeated courses of SLIT resulted in a similar increase in RGP-specific IgG2 in serum corresponding with increased frequency of IgG2+ memory B cells in the blood. However, it must be noted that the increases of IgG2+ and IgG4+ circulating B cell frequencies concern total and not allergen-specific cells and thus should not be over interpreted.

The effector mechanisms that can be triggered by antibodies due to complement activation, antibody-dependent cellular cytotoxicity, immune complex formation differ between the different immunoglobulin subclasses. IgG1 and IgG3 can efficiently trigger the classical route of complement activation, while IgG2 and IgG4 do so less efficiently or only under certain conditions for IgG2.[3] IgG2 and IgG4 that show reduced affinity to a number of FcγR. Additionally, IgG2 and IgG4 have very limited ability to elicit antibody-dependent cell-mediated cytotoxicity.[4]

The effect of AIT on IgG2 production has not been extensively reported and IgG2 was not measured on most of the studies. In this study, Heeringa et al. demonstrated that SLIT increased RGP-specific IgG2 after three consecutive courses. This suggests that repeated or high dose exposure to RGP from SLIT is required to enhance RGP- specific IgG2 beyond levels that are generated in response to annual RGP exposure during the pollen season. Furthermore, sublingual administration of RGP may have preferentially induced an IgG2 response not seen from environmental exposure through the airway. However, the immune mechanisms by which allergen-specific IgG2 may contribute to the benefits of immunotherapy remain unclear. IgG2 has been shown to inhibit histamine release from basophils by activating FcγRIIb and may reduce allergic symptoms by this mechanism. In a similar manner to IgG4, IgG2 may also bind allergen and prevent effector cell degranulation by masking IgE epitopes.

Previously, both SCIT[7] or SLIT[9], have been demonstrated to result in increased allergen-specific IgG4 serum levels. Increased allergen-specific IgG4 has been postulated as one of the explanations for the beneficial effects of immunotherapy and has been observed as a natural effect in bee-keepers exposed to bee-venom for prolonged periods, yet the exact desensitizing effect of specific IgG4 in immunotherapy remains unclear. Allergen-specific IgG4 can competitively inhibit IgE from binding to allergens and may subsequently reduce allergic responses by preventing FcεR-mediated activation of granulocytes.[9]

In contrast to IgG2, there are several features of IgG4 that may contribute to its non-inflammatory role. The two arms of IgG4 have the ability to separate and repair by means of dynamic Fab arm exchange, which leads to the production of bispecific antibodies that

are functionally monomeric. Furthermore, IgG4 is capable of inhibiting immune-complex formation by other isotypes, giving this isotype anti-inflammatory characteristics.[5-6]

Plasma cells are the cell that produce IgG2 and IgG4 antibodies but the majority of IgG-producing plasma cells are residing in the bone marrow. For this reason, the authors focused primarily on memory B cells, which are abundantly present in the blood due to their circulatory nature. These cells have the capacity to quickly differentiate into plasma cells in response to recall antigen exposure.

It is highly possible that the decrease in the IgE/IgG4 ratio during AIT is influenced by the skewing of the T cell population from allergen-specific TH2 to Treg cells as well as by increases in the number of Breg cells. IL-10, which is produced by both Tregs and Bregs, is a potent suppressor of both total and allergen-specific IgE while it simultaneously increases IgG4 production.[7-8] (Figure 1) In parallel with previous studies, it was also shown here that proliferation of Tregs from patients after SLIT was increased in response to *in vitro* stimulation with RGP and increased IL-10 production induces Ig class switching of allergen-specific B cells to IgG4.[9] B regulatory cells (Breg) and monocyte-derived macrophages may also be a substitute source of IL-10 in in vitro studies, further enhancing IgG4 class switching in response to RGP.

Figure 1. Mechanisms of AIT.

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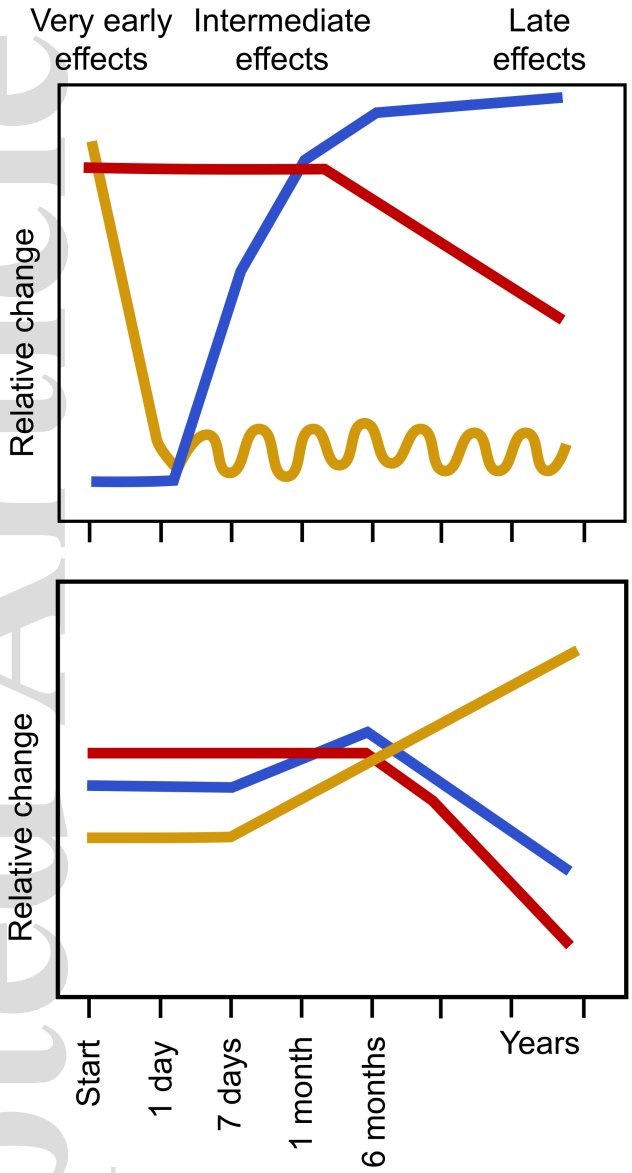

Very early basophil tolerance,
early decrease in mast cell
and basophil activity
for systemic anaphylaxis

Induction of Treg and Breg cells
Suppression of Th2-Th1 cells

Late decrease in tissue mast cells
and eosinophils and release of their mediators
Decrease in skin late-phase response

Late decrease in type I skin test reactivity

Early increase in specific IgE
followed by a late decrease in specific IgE

Increase in specific IgG4

Present study findings in SLIT:
- IgG2 (4 months)
- IgG4 (4 months)
- Treg

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